From: Hupp, Sydney [mailto:hupp.sydney@epa.gov]
Sent: Monday, May 22, 2017 3:33 PM
To: Stanko, Joseph
Cc: Dickerson, Aaron
Subject: RE: Meeting Request

Thank you!

Sydney Hupp

Executive Scheduler

Office of the Administrator

202.816.1659 (c)

From: Stanko, Joseph [mailto:jstanko@hunton.com]
Sent: Monday, May 22, 2017 2:02 PM
To: Hupp, Sydney <hupp.sydney@epa.gov>
Cc: Dickerson, Aaron <dickerson.aaron@epa.gov>
Subject: RE: Meeting Request

Sydney:

Thanks, I know the Administrator's schedule is complicated enough, but with international travel it's an additional degree of difficulty.

I'll vet this promptly from my end and respond back.

Thanks, much appreciated.

Regards,

Joe

 **Joseph Stanko**

Partner

jstanko@hunton.com
p 202.955.1529

bio | vCard

Hunton & Williams LLP
2200 Pennsylvania Avenue, NW
Washington, DC 20037

hunton.com

From: Hupp, Sydney [mailto:hupp.sydney@epa.gov]
Sent: Monday, May 22, 2017 1:14 PM
To: Stanko, Joseph
Cc: Dickerson, Aaron
Subject: RE: Meeting Request

My sincere apologies for the delay Mr. Stanko, was trying to sort out his departure for international travel. Do you have any availability left on the 2nd?

Thank you!

Sydney Hupp

Executive Scheduler

Office of the Administrator

202.816.1659 (c)

From: Stanko, Joseph [mailto:jstanko@hunton.com]
Sent: Friday, May 19, 2017 1:37 PM
To: Hupp, Sydney <hupp.sydney@epa.gov>
Cc: Jackson, Ryan <jackson.ryan@epa.gov>
Subject: RE: Meeting Request

Sidney:

Would it be possible for you to let me know if the June 2nd or June 5th would work for Administrator Pruitt? Mr. Ziemba is happy to work with other dates, but if the June 2nd and 5th are off the table, it will be helpful to know for other scheduling needs.

Thanks for all your assistance.

Joe

 **Joseph Stanko**

Partner

jstanko@hunton.com

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Washington, DC 20037

hunton.com

From: Stanko, Joseph
Sent: Monday, May 15, 2017 5:50 PM
To: 'hupp.sydney@epa.gov'
Cc: Ryan Jackson (jackson.ryan@epa.gov)
Subject: FW: Meeting Request

Dear Sydney:

I would like to request a meeting with the Administrator for Larry Ziemba, Executive Vice President, Refining, for Phillip 66. Larry has responsibility for the company's refining operations and serves in a leadership position with the American Fuels and Petrochemical Manufacturers Association. He has been working with other refiners and the Auto industry regarding the potential for higher octane fuels and other forward looking fuels issues. A brief bio is set forth below.

Larry is currently scheduled to be in D.C. on Friday June 2nd and Monday June 5th. If those days would not work with the Administrator's schedule, he is happy to work

with other days that would be more convenient for Administrator Pruitt.

Lawrence (Larry) M. Ziemba is executive vice president, Refining, for Phillips 66, a diversified energy manufacturing and logistics company. He has 35 years of experience in the oil and gas industry. Before joining Phillips 66 in May 2012, Ziemba previously worked for ConocoPhillips as president, Global Refining, a role he took on after serving as president, U.S. Refining, since 2003. He first joined Phillips Petroleum in 2001 after its acquisition of Tosco and was in charge of handling the integration of the refining operations during the merger with Conoco. Originally from Chicago, he started his career at Unocal's Chicago refinery in 1977. In 1988, he moved to Unocal's Los Angeles corporate headquarters as manager of planning/business development for its downstream business. In 1991, he managed the acquisition of Shell's Carson refinery and subsequently integrated the asset into Los Angeles operations. In 1997, Ziemba joined Tosco as they acquired Unocal's downstream business. In 1999, he was named vice president of Tosco's three San Francisco area refineries. In 2000, he was assigned to handle the acquisition and takeover of the Wood River refinery. He has held a number of industry and community leadership positions including board positions with American Fuels and Petrochemical Manufacturers Association, WRB Refining LP and the Western States Petroleum Association. Ziemba earned a bachelor's degree in mechanical engineering from the University of Illinois-Champaign in 1977 and a Master of Business Administration degree from the University of Chicago in 1985.

Thank you for your consideration,

Joe Stanko

 **Joseph Stanko**

Partner

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To: Yamada, Richard (Yujiro)[yamada.richard@epa.gov]; Beck, Nancy[Beck.Nancy@epa.gov]; Jackson, Ryan[jackson.ryan@epa.gov]
Cc: Segal, Scott[scott.segal@bracewell.com]; Lee, John[john.lee@bracewell.com]
From: Krenik, Edward
Sent: Mon 6/26/2017 9:58:57 PM
Subject: DPE Letter to Pruitt
Letter to EPA 20170626.pdf
RE_Chloroprene_Report_June 2017.pdf

Good afternoon,

Look forward to seeing you this week. Attached is a letter that was sent to the Administrator today as well as our environment assessment/report. The Request for Correction will be filed today or tomorrow.

I wanted to get this to you before our meeting so that if you have any questions we can get additional information ready for our meeting this week.

See you on the 28th. I know our CEO is looking forward to working with EPA to resolve this issue.

Thanks again,

Ed

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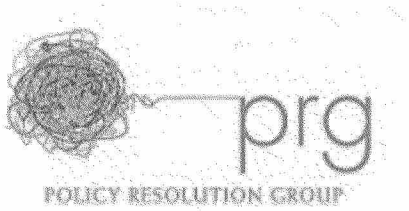

Denka Performance Elastomer LLC
560 Highway 44
LaPlace, LA 70068

June 26, 2017

The Honorable Scott Pruitt
Administrator
U.S. Environmental Protection Agency Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N.W.
Mail Code: 1101A
Washington, D.C. 20460

Re: Request to Withdraw and Correct the 2010 IRIS Review of Chloroprene

Dear Administrator Pruitt:

I write on behalf of Denka Performance Elastomer LLC (DPE) in support of the request that the U.S. Environmental Protection Agency (EPA) withdraw and correct its Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene (EPA/635/R-09/010F, 2010) (the 2010 IRIS Review). The errors in the 2010 IRIS Review threaten the very survival of DPE's Neoprene production facility in LaPlace, Louisiana (Facility). In particular, based on those errors and EPA's subsequent flawed determinations concerning the risks caused by Facility emissions, EPA is making stringent air pollution control demands concerning the Facility that are technologically impossible to achieve. EPA must expeditiously apply good science in this matter in order to alleviate the public's undue concerns about the risks associated with this Facility and to prevent further significant damage to DPE's business.

Key conclusions of the 2010 IRIS Review are not based on the best available science or sound scientific practices. First, the 2010 IRIS Review rejected the findings of the strongest available epidemiological study, which concluded that there is no increased risk of cancer in workers exposed to chloroprene (some of the study cohorts actually exhibited a *lower* risk of cancer than the control population). Rather than accepting the overall study conclusions, the 2010 IRIS Review relied on select statistically non-significant comparisons of cancer incidence rates among subgroups of the larger epidemiology study to bolster its classification of chloroprene as "likely to be carcinogenic to humans." Second, the 2010 IRIS Review is flawed because it relied on laboratory animal studies, and then used the results for the most sensitive laboratory animal – female mice – as the basis for a series of overly conservative calculations to develop the human inhalation unit risk (IUR). Contrary to sound scientific practice, the 2010 IRIS Review ignored the known differences between humans and a select strain of female laboratory mice, and relied on results in those female mice to estimate an IUR for humans. Third, the 2010 IRIS Review gives chloroprene, which EPA designates only as a "likely" and not a "known" human carcinogen, the fifth highest IUR estimate of any similar chemical, including known human carcinogens, in the IRIS database. DuPont, the former Facility owner, provided similar information and analysis to EPA in comments on the draft IRIS Review, which comments were rejected in 2010. DPE's Request for Correction and the Ramboll Environ report provide new information and weight-of-evidence review not available in 2010.

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LaPlace, LA 70068

After EPA published the 2010 IRIS Review, the National Academies of Sciences' National Research Council (NRC) recommended major reforms in the IRIS process. Congress has repeatedly instructed EPA to implement the NRC's recommendations, and EPA has advised Congress that it is doing so. The 2010 IRIS Review is plagued with flaws similar to those that gave rise to these reform initiatives, and it is extremely important that the 2010 IRIS Review now be corrected in light of its scientific and procedural deficiencies.

These issues are more fully explained in DPE's Request for Correction and in the supporting toxicological and epidemiological expert review prepared by prominent scientists with the consulting firm of Ramboll Environ: Drs. Kenneth Mundt, Robinan Gentry, and Sonja Sax. Their report is entitled *Basis for Requesting Correction of the U.S. EPA Toxicological Review of Chloroprene*, dated June 2017 ("the Ramboll Environ Report," and attached hereto). The Ramboll Environ Report identifies multiple substantive errors in the 2010 IRIS Review and demonstrates that if chloroprene is to be treated as a possible human carcinogen, the 2010 IRIS Review establishes an IUR that is 156 times too high.

By way of background, DPE acquired the Neoprene Facility from DuPont on November 1, 2015. Neoprene is a synthetic rubber utilized in a wide variety of applications, including laptop sleeves, orthopedic braces, electrical insulation, and automotive fan belts. DPE is the only manufacturer of Neoprene in the United States. The Facility is a commercial mainstay of LaPlace, Louisiana. With an annual payroll of $33 million, DPE directly employs 200-250 people in manufacturing jobs and regularly employs between 125 and 150 contractors. DPE also has created 16 new corporate jobs. Additionally, DPE is investing and upgrading the Facility, including taking new measures to reduce its environmental footprint and improve its productivity and competitiveness.

The base feedstock for Neoprene is chloroprene. The Facility's air permits authorize it to emit chloroprene, and the Facility operates in compliance with those permit limits. However, shortly after DPE's acquisition of the Facility, on December 17, 2015, EPA publicly released its 2011 National Air Toxics Assessment (NATA), which identified the Facility as creating the greatest offsite risk of cancer of any manufacturing facility in the United States. The NATA findings concerning the Facility are based on the scientifically unwarranted and outdated 2010 IRIS Review and the emission profile of the Facility.

Following the public release of the NATA, EPA and the Louisiana Department of Environmental Quality (LDEQ) pressed DPE to reduce emissions to achieve an extraordinarily miniscule ambient air target concentration of 0.2 $\mu g/m^3$ for chloroprene on an annual average basis (which is intended to reflect a 100 in 1,000,000 rate of potential excess cancers in a population exposed to such concentrations continuously for 70 years). The 0.2 $\mu g/m^3$ target is based on a risk assessment that applied the erroneous and scientifically unsubstantiated IUR from the 2010 IRIS Review, and the target reflects more than a four thousand-fold reduction in the applicable Louisiana 8-hour ambient standard for chloroprene. Ramboll Environ's expert scientific opinion is that the appropriate risk-based ambient target should be 156 times larger or 31.2 $\mu g/m^3$. There is no agency rule or even proposed rule requiring the attainment of the 0.2 $\mu g/m^3$ target, yet EPA has advised DPE, LDEQ, and the public that 0.2 $\mu g/m^3$ is the appropriate target.

As a result of the flawed science embodied in the 2010 IRIS Review, and as a result of the NATA findings and the Facility's emission profile, DPE has suffered extraordinary hardship in a number of ways.

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First, despite DPE's concerns about the science behind the 2010 IRIS Review, DPE is currently spending more than $18 million on new pollution controls. On January 6, 2017, DPE entered into an Administrative Order on Consent with LDEQ to reduce chloroprene emissions by approximately 85% below the level of the Facility's 2014 emissions. DPE estimates that the capital cost of these emission reduction devices is approximately $18 million, and the devices will cost hundreds of thousands of dollars per year to operate. Even though DPE is installing the most advanced air pollution controls available, it will still not be able to meet the stringent 0.2 $\mu g/m^3$ target.

Second, because the 2010 IRIS Review is flawed, EPA's very public announcements arising out of that Review and the NATA have created unnecessary public alarm. For example, after issuing the NATA, EPA created a public webpage specifically addressing DPE's chloroprene emissions.[1] Moreover, environmental activists and plaintiffs' lawyers have had numerous meetings in the community about DPE, all based on the faulty assumption that 0.2 $\mu g/m^3$ is the "safe" level for chloroprene. Further, a local citizen's group has formed and has been handing out misleading flyers and protesting near DPE's Facility. The erroneous IUR in the 2010 IRIS Review and the resulting NATA findings have caused DPE enormous reputational damage.

Third, as a result of the NATA findings, EPA Region 6 asked the National Environmental Investigations Center (NEIC) to investigate the regulatory compliance status of the Facility. NEIC sent a team of inspectors to the Facility from June 6-10, 2016, approximately seven months after DPE's acquisition. To be clear, DPE fully respects the important function of the EPA in enforcing environmental requirements. It is simply a fact, however, that as a result of the erroneous IUR and the NATA findings, EPA has initiated an enforcement proceeding against DPE and has devoted an extraordinary amount of resources from the Department of Justice, EPA headquarters, EPA Region 6, and NEIC to developing and pursuing the issues in the NEIC report.

Finally, since acquiring the Facility in November of 2015, DPE's relatively small management team has been buffeted by continuous environmental regulatory demands resulting from the erroneous IUR and the NATA findings. In addition to Facility operation, DPE staff has been in non-stop meetings and negotiations with EPA and LDEQ. DPE's legal and consulting expenses have been enormous, in the millions of dollars. Underlying all of these expenses and burdens on DPE is the erroneous IUR in the 2010 IRIS Review, as applied in the NATA risk assessment.

DPE needs EPA's assistance in the expeditious application of good science to this matter. In meetings with EPA in 2016 concerning the need to correct the 2010 IRIS Review, EPA officials advised DPE that EPA's "queue is full". DPE respectfully requests that EPA review the science underlying the 2010 IRIS Review, withdraw the erroneous IUR, and develop a more accurate toxicological review of chloroprene. We are confident that the Ramboll Environ Report will lead you to these conclusions. Without

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[1] *See* https://www.epa.gov/la/laplace-louisiana-background-information.

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this relief, it is uncertain whether DPE will be able to reduce emissions sufficiently to satisfy agency demands, or even continue operation.

Sincerely,

Koki Tabuchi
President and Chief Executive Officer
Denka Performance Elastomer LLC

Intended for

Denka Performance Elastomer, LLC

560 Highway 44

LaPlace, LA 70068

Document type

Final

Date

June 2017

BASIS FOR REQUESTING CORRECTION OF THE US EPA TOXICOLOGICAL REVIEW OF CHLOROPRENE

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RAMBOLL ENVIRON

CONTENTS

TABLES

FIGURES

APPENDIX

ACRONYMS AND ABBREVIATIONS

ADAF	age-dependent adjustment factor
AIC	Akaike Information Criterion
BCME	bis(chloromethyl)ether
BMD	benchmark dose
BMD10	benchmark dose at the 10% extra risk level
BMDL	lower 95% confidence limit of the benchmark dose
BMDL10	lower 95% confidence limit of the benchmark dose at the 10% extra risk level
DAF	dosimetry adjustment factor
DPE	Denka Performance Elastomer, LLC
EDB:	ethylene dibromide
F1	first generation
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
µg/m^3	microgram(s) per cubic meter
MOA	mode of action
NATA	National Air Toxics Assessment
NDMA	nitrosodimethylamine
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NTP	National Toxicology Program
PBPK	physiologically based pharmacokinetic (model)
POD	point of departure
ppm	parts per million
Ramboll Environ	Ramboll Environ US Corporation
RR	relative risk
SIR	standardized incidence ratio
SMR	standardized mortality ratio
US EPA	United States Environmental Protection Agency
VCM	vinyl chloride monomer
WHO	World Health Organization
WOE	weight of evidence

EXECUTIVE SUMMARY

Background

In 2010, the United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS) program published a review of the epidemiology and toxicology literature on chloroprene to provide scientific support and rationale for hazard and dose-response assessment in IRIS, including deriving an inhalation unit risk (IUR) and other values for chronic exposure (www.epa.gov/iris).

In the "Toxicological Review of Chloroprene" (hereafter referred to as the "2010 Review") (US EPA 2010a), US EPA concluded that chloroprene was "likely to be carcinogenic to humans" based on (1) statistically significant and dose-related information from an National Toxicology Program (NTP 1998) chronic inhalation bioassay demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) the proposed mutagenic mode of action (MOA); and (5) structural similarities between chloropren e and known human carcinogens butadiene and vinyl chloride (US EPA 2010a).

The 2010 Review d erived an IUR for lifetime exposure to chloroprene of 5 x 10^{-4} per microgram per cubic meter ($\mu g/m^3$). This is the 5th highest IUR generated by US EPA to date for any chemical (not including carcinogenic metals or coke oven emissions) classified by US EPA or the International Agency for Research on Cancer (IARC) as a known or likely/probable human carcinogen. As outlined in detail below, we have determined that US EPA's classification relied on questionable , non-transparent evaluation and interpretation of the toxicological and epidemiological evidence. Therefore, the IUR for chloroprene was not based on the best standard methods US EPA has used for other carcinogens.

The IRIS Process: Challenges, Recent Changes, and Recommendations for Improvement

The US EPA IRIS process has been subject to high-level constructive criticism. Most noteworthy, subsequent to the 2010 Review, the National Research Council (NRC) of the National Academies of Science (NAS) published a series of reports recommend ing important changes to improve the IRIS process (NRC 2011, 2014). The recommendations were well received by US EPA, but have not yet been fully implemented, and have not been applied to previously published reviews. In particular, NRC (2011, 2014) emphasized the importance of transparency and rigor in the review methods. NRC (2011) provided guidance on development of inclusion and exclusion criteria for studies , and on methods for evaluating and taking into account various forms of bias and other methodologic characteristics that could impact study findings.

While the 2010 Review meets some of these NRC recommendations , it does not meet other key standards such as the evaluation and synthesis of the epidemiological and mechanistic data , and would benefit from their consideration and application. A transparent evaluation and integration of the published

epidemiological and toxicological evidence on chloroprene carcinogenicity highlights the need to reconsider US EPA's classification of chloroprene as "likely to be carcinogenic to humans" to be in line with the weight of evidence and the International Agency for Research on Cancer's (IARC 1999) classification of chloroprene as "possibly carcinogenic."

Toxicological Evidence

US EPA should evaluate the animal toxicological data that form the basis of the estimated chloroprene inhalation unit risk (IUR) in accordance with the NRC recommendations and US EPA standard risk evaluation methodologies. US EPA relied on the animal studies conducted by the NTP that showed very little consistency across species in tumor incidence and sites. These results indicated substantial species differences and demonstrated a unique sensitivity in the female mouse, with lung tumors being the most sensitive endpoint. Thus, US EPA used the female mouse data to derive the IUR, but without fully accounting for important pharmacokinetic differences between the mouse and humans.

In addition to revisiting the reliance on the animal dataset for the estimation of the IUR, US EPA should critically re-evaluate and integrate the cytotoxic and genotoxic evidence for chloroprene. The evidence from these studies indicates that chloroprene acts through a different mode of action (MOA) than the structurally similar and known human carcinogen 1,3-butadiene. Based on an evaluation consistent with the NRC (2011, 2014) recommendations, chloroprene's genotoxicity profile lacks several attributes necessary to conclude that there is a mutagenic MOA. Instead, the evidence supports site-specific cytotoxicity as a more likely MOA, as opposed to US EPA's conclusion that chloroprene acts *via* a mutagenic MOA.

Epidemiological Evidence

It is also necessary to critically evaluate the available epidemiological evidence on occupational chloroprene exposure. US EPA evaluated the epidemiological evidence of chloroprene carcinogenicity based on several occupational cohorts from around the world. This evaluation, however, would have benefited from more transparency and rigor with regard to how individual study quality was assessed and weighted in the overall weight-of-the-evidence assessment. In particular, US EPA did not assign more weight to the most recent epidemiological study by Marsh *et al.* (2007a, b), which also is the largest and most robust study to date. This study has been rated by other scientists as the best quality study available in part because it has the most comprehensive characterization of chloroprene exposure (Bukowski *et al.* 2009). Instead, US EPA equally weighted this study with poorer quality Russian, Armenian, and Chinese studies.

Marsh *et al.* (2007a, b) reported no excess occurrence of lung or liver cancers among chloroprene exposed workers. In fact, overall and for all sub-cohorts defined by specific plant(s), standardized morality ratios (SMRs) based on local reference rates were all below 1.0, providing no indication of any excess of these cancers among chloroprene exposed workers. US EPA, however, discounted this primary finding, and instead interpreted a correlation between exposure level and risk relative to a comparison subgroup where the comparison group exhibited

anomalously fewer cancers than expected, creating the appearance of an increased risk in the higher exposure groups. Furthermore, US EPA overlooked that there were as few as two liver cancer deaths in the comparison subgroup, likely reflecting a random deficit among this group. The US EPA summary of this study indicates incomplete evaluation and misinterpretation of the published results. Properly interpreted, the evidence does not demonstrate an association between occupational chloroprene exposure and human cancer incidence.

US EPA's Derivation of the Chloroprene IUR

US EPA derived the current chloroprene IUR based on a number of assumptions that are not substantiated by the scientific evidence, contributing to overestimation of an already conservative risk estimate *(i.e.*, one based on the most sensitive species, gender, and endpoint). Specifically, US EPA based the chloroprene IUR on a composite estimate of risk based on multiple tumors observed primarily in mice, not just the lung tumors for which the data were more conclusive. US EPA then assumed that the female mouse-based IUR was representative of continuous human exposure, and that lung tumors were systemic rather than portal-of-entry effects; US EPA also rounded up at various stages of adjustment. Finally, US EPA applied an age-dependent adjustment factor (ADAF) based on insufficient data to support a mutagenic MOA.

A PBPK Model for Chloroprene

In calculating the IUR, US EPA should have used the available pharmacokinetic model for chloroprene. Himmelstein *et al*. (2004 a,b) developed a physiologically based pharmacokinetic (PBPK) model for chloroprene to help explain the divergent results observed across animal species. The model demonstrates why the mouse is the most sensitive species and why humans are likely to be comparatively much less sensitive to the effects of chloroprene exposure.

The hypothesis that differences in pharmacokinetics are determinants of the observed species differences has been demonstrated for other chemicals, including vinyl chloride. Thus, it is scientifically appropriate that US EPA employ PBPK models, which use the best available science to adjust for these differences, to derive IURs for all chemicals, such as chloroprene, for which data are available.

US EPA did not use the PBPK model developed by Himmelstein *et al*. (2004 a,b) to inform the chloroprene IUR because US EPA noted that the data required to validate the model had not been published. However, all of the quantitative data necessary to refine and verify the critical metabolic parameters for the existing peer-reviewed PBPK model for chloroprene were available at the time of the 2010 Review and could have been used. Since then, additional data have been published, and the findings validate the model (Thomas *et al.* 2013, Yang *et al*. 2012, Allen *et al*. 2014). In particular, Allen *et al.* (2014) derived an IUR based on PBPK results and the incidence of respiratory cancer that was 100 times lower than US EPA's value, using a method which integrates both the animal and human evidence. Importantly, the IUR reported by Allen *et al*. (2014) is consistent with IURs for similar compounds such as vinyl chloride and 1,3-butadiene, which have stronger and more consistent epidemiological evidence of human carcinogenicity than chloroprene.

Calculation of an Up dated Chloroprene IUR

We conducted an updated analysis by applying the results from validated PBPK models to arrive at an IUR that includes an understanding of interspecies pharmacokinetics. We applied standard US EPA methodology and conservative assumptions to estimate of the potential cancer effects of chloroprene. Our estimated IUR is 1.1×10^{-2} per ppm or 3.2×10^{-6} per $\mu g/m^3$, which is of the same order of magnitude as the IUR derived by Allen *et al*. (2014), and which better reflects the scientific understanding of potential chloroprene cancer effects in humans. These results are also consistent with the results from validated PBPK models and comparisons with other structurally relevant compounds such as vinyl chloride and 1,3-butadiene, both recognized as known human carcinogens.

There is little scientific support for each of US EPA's conservative assumptions and subsequent adjustments. Combining a fuller understanding of interspecies pharmacokinetic differences and validated PBPK models with the results from the strongest epidemiological data provides the scientific grounds for updating the 2010 IUR and calls into question the strength of the evidence to support a "likely to be carcinogenic to humans" classification . Similar adjustments should also be considered in estimating the chloroprene inhalation reference concentrations (RfC), as species- and strain-specific differences are noted . This will assure that policies and decisions resting on these toxicity values meet the test of sound science, transparent methods, and reproducible findings.

Conclusions

The IUR published in the 2010 Review requires correction . An updated IUR should be based on the best available methodology as well as a valid interpretation of the body of published evidence. Correction is critical given that the IUR published in the 2010 Review is being used by US EPA for enforcement actions.

1 INTRODUCTION

In December, 2015, the United States Environmental Protection Agency (US EPA) published the 2011 National Air Toxics Assessment (NATA), indicating a high off-site air pollution cancer risk from emissions of chloroprene from the Neoprene production facility in LaPlace, Louisiana. The previous month, on November 1, 2015, Denka Performance Elastomer, LLC (DPE), had acquired the LaPlace Neoprene production facility. The underlying NATA risk calculations combined estimated ambient chloroprene concentrations from air modeling analyses with the cancer inhalation unit risk (IUR) value derived by the US EPA Integrated Risk Information System (IRIS) and documented in the Toxicological Review of Chloroprene (hereafter referred to as the "2010 Review") (US EPA 2010a).

On behalf of DPE, Ramboll Environ US Corporation (Ramboll Environ) prepared this summary review of the US EPA toxicity assessment for chloroprene, focusing on a detailed review of US EPA's derivation of the cancer IUR reported in the 2010 Review (US EPA 2010a). US EPA's chloroprene risk assessment calculations are based on and directly proportional to US EPA's IUR for lifetime exposure to chloroprene of 5×10^{-4} per micrograms per cubic meter ($\mu g/m^3$). The chloroprene IUR is the 5th highest IUR generated to date for any substance classified by US EPA or the International Agency for Research on Cancer (IARC) as a known or likely/probable human carcinogen (not including carcinogenic metals or coke oven emissions). The chloroprene IUR is orders of magnitude higher than IURs derived by US EPA for substances, such as vinyl chloride, 1,3-butadiene, and benzene, that have been classified by US EPA as known human carcinogens.[1] In contrast, chloroprene has been classified as "likely to be carcinogenic to humans" based on a weight-of-evidence (WOE) assessment that included an animal inhalation study conducted by the National Toxicology Program (NTP 1998) and four (of nine) epidemiological studies reportedly indicating increased risks for liver cancer (US EPA 2010a). It was noted that these data were insufficient to classify chloroprene as a known human carcinogen. On the other hand, IARC classified chloroprene as "possibly carcinogenic to humans," based on the same evidence from experimental animal studies and similar epidemiological evidence concluded that the human evidence was inadequate (IARC 1999).

Since the 2010 Review (US EPA 2010a), the National Academies of Sciences National Research Council (NRC 2011, 2014) has recommended substantive improvements to the IRIS evaluation process, calling for greater transparency including improved methods for and documentation of scientific study selection, critical review of study quality and limitations, and the synthesis of findings across studies. This has provided much of the impetus for changes to the IRIS process. Improvements in the critical evaluation of epidemiological study quality and bias were noted as especially important, as statistical associations in epidemiological studies are only meaningful if supported by rigorous study design and data quality control. In addition, NRC noted the need for improved approaches to integrating evidence across diverse lines of investigation —including evidence from animal

[1] https://www.epa.gov/fera/dose-response-assessment-assessing-health-risks-associated-exposure-hazardous-air-pollutants

experiments, mechanistic investigations and epidemiological studies —in drawing conclusions regarding carcinogenicity and in deriving unit risk factors for cancer. NRC recommended better evidence integration that considers and weighs the entire body of scientific evidence, and that does not rely on select and unrepresentative findings (NRC 2011, 2014). Similarly, using formaldehyde as an example, NRC recommended improved use of evidence in risk assessments. NRC (2011) recommended using physiologically based pharmacokinetic (PBPK) models to quantify demonstrated differences in pharmacokinetics across species, and further recognized PBPK models as a tool to support extrapolations between species, thereby reducing the uncertainty in quantitative risk assessments (NRC 2014). These NRC recommendations remain highly relevant to the evaluation of chloroprene. In **Section 2**, we highlight key recommendations made by the NRC for improvements to the IRIS process that potentially impact the chloroprene evaluation.

Consistent with the NRC recommendations to improve the scientific quality and validity of the 2010 Review, US EPA needs to address significant uncertainties associated with the derivation of the IUR. These uncertainties pertain to the human relevance of the animal evidence, and whether or not various cancer types observed in animal experiments should be combined in estimating potential cancer risk to humans. Studies available both at the time of the 2010 Review, and published since, demonstrate clear and significant pharmacokinetic differences between humans and animals (Himmelstein *et al.* 2004a, b; Yang *et al.* 2012; Thomas *et al.* 2013; Allen *et al.* 2014). These differences must be considered in order to derive a scientifically valid human cancer unit risk for chloroprene based on animal studies. In **Section 3**, we discuss the uncertainties associated with toxicological evidence; and in **Section 4** we propose that the available mechanistic evidence supports a cytotoxic, rather than mutagenic, MOA for chloroprene.

In **Section 5**, we discuss US EPA's evaluation of the epidemiological data. US EPA did not fully or accurately summarize the findings from the Marsh *et al*. (2007a, b) study, which represents the largest and most comprehensive epidemiological study of chloroprene to date. Marsh *et al*. (2007a, b) reported no evidence of increased risks of liver and lung cancer with occupational chloroprene exposure; however, US EPA drew contrary conclusions from small subsets of the Marsh *et al*. (2007a, b) data.

In **Section 6**, we discuss the uncertainty associated with the evidence presented by US EPA to support a classification of "likely to be carcinogenic to humans," noting that the weight of evidence narrative is incomplete and the evidence is weaker than US EPA reports, and is more consistent with a "suggestive" classification.

In **Section 7**, we summarize the uncertainties associated with the US EPA derivation of the IUR, and in **Section 8**, we compare the IUR for chloroprene to other chemicals that have been classified by US EPA and IARC as known or probably human carcinogens. This comparison shows that the IUR for chloroprene is substantially out of line with the US EPA risk evaluation of chemicals that are known carcinogens.

In **Section 9**, we summarize new evidence that indicates that a PBPK model is the most valid and appropriate means of quantifying the large differences between animal and human responses to chloroprene exposure and in **Section 10**, we use PBPK results and standard US EPA methods endorsed by NRC to calculate an IUR for chloroprene. In **Section 11**, we use exposure data from the Marsh *et al.* (2007a, b) study to calculate the expected incidence of cancer among workers using the 2010 US EPA IUR and using PBPK-adjusted IURs as a "reality check" to demonstrate that the PBPK-adjusted IUR, but not the US EPA-derived IUR, is consistent with the epidemiological findings.

In **Section 12** we discuss the need to apply pharmacokinetic modeling in the derivation of the RfC, which also suffers from application of default methodology that does not properly account for the known pharmacokinetic differences across species, and species- and strain-specific differences in response.

Lastly in **Section 13**, we conclude that an updated and corrected IRIS assessment, and especially an updated IUR, are warranted and urgently needed. The new assessment should combine the most up-to-date scientific evidence regarding chloroprene toxicity and carcinogenicity with improved and more transparent methods for conducting toxicological and epidemiological reviews, in accordance with the NRC recommendations and guidance (NRC 2011, 2014). We are confident that the substantive and procedural reasons for updating the IRIS assessment for chloroprene, as detailed in this report, will result in a valid and scientifically appropriate IUR for chloroprene that is also consistent with the assessments for other substances including several known human carcinogens.

2 THE IRIS PROCESS: CHALLENGES, RECENT CHANGES, AND NRC RECOMMENDATIONS FOR IMPROVEMENT

2.1 Purpose of the IRIS program

The IRIS program was developed to be the primary source of toxicological information for federal, state, and international regulatory agencies for setting risk-based regulatory standards. It was intended to provide consistency among toxicological assessments within US EPA. IRIS assessments contain hazard evaluations (determinations of whether substances are capable of causing disease) and dose-response assessments (determinations of the levels at which such effects occur) for various chemicals, including cancer and non-cancer outcomes.

2.2 Challenges in the IRIS process

While most of the IRIS assessments have been straightforward and well documented, others have proved to be more complex and challenging, sometimes lacking transparency of methods. These problems have led to significant variability and uncertainty regarding the calculated estimates of hazard or risk of health effects in humans. As a consequence, the NRC has been called on multiple times to review some of the more challenging or ambiguous assessments, including those for formaldehyde, dioxin, and tetrachloroethylene.

In perhaps the most critical evaluation, the NRC (2011) reviewed the draft "Toxicological Review of Formaldehyde - Inhalation Assessment" (US EPA 2010c) and outlined several general recommendations for the IRIS process, as well as some specific aspects needing improvement. Subsequently, Congress held several hearings regarding the IRIS program. A House Report (112-151) that accompanied the Consolidated Appropriations Act of 2012 (Public Law 112-74)[2] specified that as part of the IRIS process, US EPA had to incorporate the recommendations of NRC in its IRIS "Toxicological Review of Formaldehyde" where appropriate, based on chemical-specific information and biological effects. Congress requested that NRC oversee this process to ensure US EPA implemented the changes. Congress also directed that NRC should make additional recommendations as needed to further improve the program. In 2014, NRC released a report on the IRIS process, which largely described the findings in its 2011 formaldehyde review as they relate more broadly to the IRIS process (NRC 2014). The final Toxicological Review of Formaldehyde has not yet been released.

Subsequently, US EPA published a report entitled "Integrated Risk Information System (IRIS) Program: Progress Report and Report to Congress" (US EPA 2015) in which US EPA assured Congress that progress toward improving the IRIS process and addressing the NRC recommendations was continuing.

NRC (2011, 2014) also emphasized the importance of a detailed protocol, including making the methods and the process of the review transparent. Increased transparency provides not only the opportunity for meaningful peer review, but also

[2] Pub. No. 112-74, Consolidated Appropriations Act, 2012 available at https://www.gpo.gov/fdsys/pkg/PLAW-112publ74/pdf/PLAW-112publ74.pdf

for other investigators to verify the methods and replicate findings. The protocol should specify how studies will be evaluated and weighted according to quality rather than on the basis of findings; explicitly state the inclusion and exclusion criteria for studies ; describe how study quality will be evaluated ; and outline methods for evaluating and taking into account various forms of bias and other methodologic characteristics of the studies that could impact their respective conclusions. The 2010 Review did not follow such a protocol.

Another key criticism that the NRC (2011) made specific to the IRIS assessment of formaldehyde, and more generally to the IRIS program as a whole, was that the IRIS process lacked an appropriate framework for systematic review and integration of all applicable lines of evidence. NRC (2011) cited the systematic review standards adopted by the Institute of Medicine (2011) as being appropriate for such an analysis.

2.3 Recommendations for improvement of the IRIS process in updating the 2010 Review

Because the 2010 Review predates the NRC critique , it would benefit from application of many of their recommendations. For example, clearer descriptions of how the epidemiological evidence was evaluated would provide greater transparency. Similarly, epidemiological evidence should be evaluated for study quality and assessed for potential bias , as some of the strongest epidemiological evidence was misinterpreted (*i.e.*, from the Marsh *et al.*, 2007a, b studies), and results from some weaker studies (from Russia, Armenia, and China) were given equal weight .

US EPA's Guidelines for Carcinogen Risk Assessment (US EPA 2005) established study quality criteria for the WOE evaluation and for identifying and justifying the use of specific epidemiological studies in assessing evidence of carcinogenicity, as follows :

- Clear objectives
- Proper selection and characterization of comparison groups (cohort and reference)
- Adequate characterization of exposure
- Sufficient duration of follow-up
- Valid ascertainment of causes of cancer morbidity and mortality
- Proper consideration of bias and confounding
- Adequate sample size to detect an effect
- Clear, well-documented and appropriate methods for data collection and analysis
- Adequate response (minimal loss to follow -up)
- Complete and clear documentation of results

These points were similarly outlined in the NRC critique of the IRIS process (NRC 2014).

Based on a critical review of the animal toxicology evidence, important differences in chloroprene toxicity have been demonstrated across species that are explained by differences in pharmacokinetics. In such circumstances PBPK models are required to adjust for these differences and have been applied by US EPA for other chemicals. Although a chloroprene-specific PBPK model was available at the time of the 2010 Review, US EPA did not use it. Since the release of the 2010 Review, additional data and a fully validated PBPK model have been peer-reviewed and published. By incorporating the highest quality epidemiological studies and the most recently published data on the pharmacokinetics of chloroprene metabolism, deriving a scientifically sound IUR for chloroprene is straightforward. As demonstrated below, an IUR derived using methods applied by US EPA and the scientifically highest quality data publically available will produce an IUR that is over 150 times lower than the IUR published in the 2010 Review.

3 TOXICOLOGICAL WEIGHT OF EVIDENCE: ANIMAL STUDIES

3.1 Guidelines for evaluating toxicological studies

US EPA set forth criteria for the evaluation of toxicological data in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005). These guidelines are largely consistent with the NRC recommendations for IRIS (NRC 2014). However, US EPA did not apply these risk assessment guidelines in the 2010 Review in its evaluation and determination of the weight of evidence (WOE) available from the animal, mechanistic, and epidemiological studies of chloroprene. In this section, we discuss the toxicological evidence available to evaluate whether it supports carcinogenicity of chloroprene in humans.

3.2 Animal studies show important pharmacokinetic differences across species

US EPA based the 2010 IRIS IUR estimate for chloroprene primarily on the findings of a two-year inhalation study conducted by the NTP (1998). The NTP (1998) study found statistically significant increases in tumor incidence at multiple sites in the B6C3F1 mice, including: all organs (hemangiomas and hemangiosarcomas), lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin, liver, and mammary glands. With increasing exposures, the tumors generally appeared earlier, and statistically significant pair-wise comparisons were reported with increasing exposure level. F344/N rats were less sensitive to chloroprene exposures than B6C3F1 mice.

US EPA also considered results from another large study conducted by Trochimowicz *et al.* (1998) in Wistar rats and Syrian hamsters that showed a large variability in the tumor incidence and sites across species. Trochimowicz *et al.* (1998) found that although tumors appeared across multiple sites in both rats and hamsters, there were no statistically significant increases at any particular site, no significant trends observed with increasing concentration, and tumor incidence in less than 20% of hamsters. These results showed that the Wistar rat and the hamster are less sensitive to the toxicity of chloroprene than B6C3F1 mice or F344/N rats.

The results of the NTP (1998) and Trochimowicz *et al.* (1998) studies indicated that the mouse is the most sensitive species to chloroprene among the species tested, based on the concentrations at which statistically significant increases in tumor incidence were observed, as well as the number of tumor sites. In the NTP (1998) study, the incidence of lung tumors was observed to be statistically significantly elevated at the lowest exposure tested (12.8 parts per million [ppm]) in both female and male mice. Statistically significantly increased lung tumor incidence was not observed in any other animal species that was evaluated, including male and female rats administered chloroprene at concentrations up to 80 ppm. For other tumor sites, there were some statistically significantly elevated results in B6C3F1 mice and F344/N rats, but primarily limited to the highest exposure levels (80 ppm). For example, the incidence of liver tumors in mice were only statistically significantly increased in female mice at the highest exposure concentration tested

(80 ppm). For these reasons, the 2010 Review noted that the differences in response observed between the NTP (1998) and Trochimowicz *et al*. (1998) studies may be due to species and/or strain differences.

Thus, across all tested species, the data demonstrated that mice are the species most sensitive to chloroprene exposure and that the incidence of lung tumors is the most sensitive endpoint in mice. The findings therefore are specific to mice and not generalizable across animal species. Given the differences in response in the mouse as compared to other laboratory species following chloroprene exposure, it is particularly important to evaluate the potential for differences in pharmacokinetics to better characterize and explain the cross-species differences, particularly in developing an IUR intended to be predictive of human risk.

3.3 Conclusions

US EPA derived a chloroprene human IUR based not only on the highest IUR, which corresponded with the lung tumors (the most sensitive endpoint) and female mice (the most sensitive species and gender), but also, as discussed below, US EPA then calculated a human composite IUR that was based on multiple tumor sites in the female mouse. Rats were considerably less sensitive to the carcinogenic effects of chloroprene and thus were not considered further in the dose-response analysis; however, the observed lower incidence of tumors in rats than mice indicates significant species differences that cannot be disregarded in the human carcinogenicity evaluation.

4 MECHANISTIC EVIDENCE: CHLOROPRENE MODE OF ACTION

4.1 Guidelines for evaluating mechanistic studies

As with the evaluation of animal data, US EPA did not apply the guidelines for evaluation of mechanistic weight of evidence set forth in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) and the NRC recommendations for IRIS (NRC 2014). In this section, we discuss the mechanistic evidence available to evaluate whether it supports a mutagenic mode of action (MOA) for chloroprene.

4.2 Mechanistic evidence for cancer effects from chloroprene do not support a mutagenic MOA

A key determinant of understanding whether an agent is carcinogenic is to establish an MOA. In the 2010 Review, US EPA hypothesized that chloroprene "acts via a mutagenic MOA involving reactive epoxide metabolites formed at target sites or distributed systemically throughout the body." US EPA noted that "this hypothesized MOA is presumed to apply to all tumor types" (US EPA 2010a), suggesting some non-independent events would be needed for the development of all of the tumors observed. In formulating this hypothesis of a mutagenic MOA, the 2010 Review did not present a description of whether or how the available evidence was critically evaluated, weighted and integrated. This is inconsistent with US EPA (2005) guidelines which indicated that the purpose of the hazard assessment is to "construct a total analysis examining what the biological data reveal as a whole about carcinogenic effects and MOA of the agent, and their implications for human hazard and dose-response evaluation." These 2005 guidelines are also consistent with the new NRC (2014) recommendations for the need for integration of the evidence to support scientific conclusions.

In providing supporting evidence for a mutagenic MOA, the 2010 Review focused on *in vitro* studies (using different exposure systems) in bacteria, with less weight placed on the results from *in vitro* studies in mammalian cells and *in vivo* studies.[3] In particular, in assessing whether chloroprene has a mutagenic MOA, the 2010 Review gave little weight to the studies conducted by the NTP and others (Tice 1988, Tice *et al*. 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995). This also is contrary to the recommendations of NRC (2014) regarding evidence integration. The NTP (1998) study that served as the basis of the US EPA IUR for chloroprene states, "chloroprene was not mutagenic in any of the tests performed by the NTP."

Furthermore, the majority of the conventional genetic toxicology studies relied on in the 2010 Review did not report positive results following administration of chloroprene. In drawing conclusions concerning the chloroprene MOA, US EPA should have acknowledged the flaws and methodological limitations in the studies on which it relied. When these studies and their limitations are considered, along with the predominantly negative *in vitro* and *in vivo* genotoxicity tests, there is little evidence for concluding that chloroprene is mutagenic or genotoxic (NTP 1998, Pagan 2007). Therefore, this evidence should not be used to support a

[3] *In vitro* mammalian and *in vivo* studies are generally considered to be more relevant to effects that might be observed in humans (*e.g.*, Wetmore *et al.* 2013).

classification of chloroprene as a "likely" human carcinogen and should not influence the derivation of the chloroprene IUR.

In summary, the hypothesized MOA was based on four major assumptions by US EPA (2010a):

1. There are similarities in the MOA for the known human carcinogen 1,3-butadiene, which involves metabolism to a reactive epoxide intermediate
2. Chloroprene forms DNA adducts via its epoxide metabolite
3. Chloroprene is a point mutagen *in vitro*
4. Chloroprene is a point mutagen *in vivo*

However, the integration of the currently available evidence for chloroprene support none of these assumptions. A discussion of why the available science is inconsistent with these assumptions is provided in the following sections.

4.2.1 The chloroprene mutagenic profile is distinct from that of 1,3-butadiene

US EPA assumed that chloroprene has a similar MOA to that of 1,3-butadiene, which is metabolized to epoxide intermediates and is a rodent carcinogen. While both compounds may be carcinogenic in rodents, evidence is available that shows that the mutagenic and clastogenic profiles of 1,3-butadiene are considerably different from the profile of chloroprene (Tice 1988, Tice *et al.* 1988). Unlike 1,3-butadiene, chloroprene does not induce effects when tested in standard *in vivo* genotoxicity screening studies in mammals (Table 4.1). Although the reactive metabolite of chloroprene (1-chloroethenyl) oxirane does induce mutations *in vitro* in bacterial strains (Himmelstein *et al.* 2001a), neither the administration of chloroprene nor the reactive epoxide metabolite was genotoxic or mutagenic in *in vitro* mammalian cells, including Chinese hamster V79 cells (Himmelstein *et al.* 2001a, Drevon and Kuroki 1979). Also, unlike 1,3-butadiene, chloroprene was not genotoxic when tested *in vivo* (Tice 1988, Tice *et al.* 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995).

Table 4.1. Comparison of the Mutagenic Profiles of Chloroprene and 1,3-Butadiene

Chemical	In Vitro Ames	In Vivo (B6C3F1 mouse)a		
		CA	SCE	Micronuclei
1,3-Butadiene	+	+	+	+
Chloroprene	+/-	-	-	-

a Exposure was 10-12 days (6 hr/day) inhalation (Tice 1988)

These findings indicate that the reactive metabolites formed from chloroprene are effectively detoxified *in vivo* in the concentration ranges studied. This is an important difference between chloroprene and 1,3-butadiene. In addition, 1,3-butadiene appears to be an effective somatic cell genotoxin in mice (Tice 1988), whereas chloroprene was not genotoxic in *in vivo* assays (Tice 1988, Tice *et al.*

1988, Shelby 1990, Shelby and Witt 1995, NTP 1998). The only published chloroprene-related study showing positive chromosomal aberrations *in vivo* was a study cited by Sanotskii (1976); but as acknowledged in the 2010 Review, this study was technically deficient and conflicted with stronger and more recent studies conducted by NTP in mice (Shelby 1990, NTP 1998).

Two other major differences between these chemicals are evident from the experimental data. First, the *ras* profile in lung tumors in treated animals is considerably different for chloroprene and 1,3-butadiene (Sills *et al.* 1999). Secondly, the toxic effects and histopathology observed in chloroprene-treated F344 rats and B6C3F1 mice are substantially different from those seen in 1,3-butadiene exposed animals (Melnick *et al*. 1996). These differences in toxic effects and histopathology suggest that the carcinogenic MOA for 1,3-butadiene also is different from that of chloroprene.

Furthermore, even if we disregard the assumption that chloroprene acts *via* a similar MOA as 1,3-butadiene, the chloroprene IUR is more than an order of magnitude greater than that of 1,3-butadiene. This is inconsistent with the assumption that these compounds have a similar MOA, and is also inconsistent with US EPA's underlying assumptions regarding the carcinogenicity and the potency of chloroprene relative to 1,3-butadiene.

4.2.2 Evidence does not support the formation of DNA adducts by chloroprene metabolism to an epoxide intermediate in vitro

The 2010 Review assumed that the chloroprene epoxide metabolite (1-chloroethenyl)oxirane forms DNA adducts. There is little evidence that this occurs *in vivo*. Although *in vitro* studies suggest an interaction between this metabolite and DNA adducts, this effect has not been confirmed *in vivo*. In addition, the lack of any observed genotoxicity *in vivo* as described above (Tice 1988, Tice *et al*. 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995) does not support an interaction between chloroprene and DNA *in vivo*.

4.2.3 Evidence does not support mutagenicity of chloroprene in vitro

The 2010 Review also assumed that chloroprene is a point mutagen *in vitro*. However, the results of the bacterial mutagenicity studies are equivocal, at best, and the findings from the Ames tests question the classification of chloroprene as a mutagen (NTP 1998, Pagan 2007). The results from two studies indicated that chloroprene was mutagenic in *Salmonella typhimurium* TA100 and/or TA1535, particularly with the addition of S9 mix, which incorporates the metabolism of chloroprene (Bartsch *et al*. 1979, Willems 1980). Two other studies failed to show any increase in TA1535 or TA100 revertants, as shown in Table 4.2. Chloroprene was not mutagenic in *S. typhimurium* strains TA98 or TA1537 (Zeiger *et al*. 1987). Because toxicity to the Salmonella cells was reported for all of the studies, one can assume there was adequate exposure to chloroprene and its metabolites or oxidative degradation products, although concentrations and composition verification were not performed.

Table 4.2. Ames Test Results for Chloroprene with TA1535 and/or TA100

Study	Method	Exposure	Response	
			With S9 mix	Without S9 mix
Bartsch *et al*. 1979	Desiccator [a]	4 hours	++	+
Westphal *et al*. 1994	Pre-inc[b]	2 hours	-	-
NTP 1998	Pre-inc[b]	20 minutes	-	-
Willems 1980	Desiccator [a]	24-48 hours	++	+

[a] Plates sealed in desiccator at 37° C with tops removed.

[b] Chemical added to sealed tubes and mixed at 37° C.

Toxicity results further appear to be dependent on the exposure methods and the form of chloroprene tested *(e.g.*, newly distilled or aged). Westphal *et al*. (1994) confirmed the importance of both vehicle and decomposition products in assessing the mutagenicity of chloroprene. For example, they showed that freshly distilled chloroprene was not mutagenic, but chloroprene aged for as little as two to three days at room temperature was mutagenic in *S. typhimurium* TA100. The mutagenicity increased linearly with the age of the distillate, probably due to the presence of decomposition products such as cyclic dimers (Westphal *et al.* 1994). Therefore, it is not possible to conclude from published data that chloroprene is a point mutagen in bacteria.

Chloroprene also does not appear to be mutagenic in mammalian cells. Drevon and Kuroki (1979) were not able to induce point mutations when chloroprene was tested in Chinese hamster V79 cells. The results for mammalian cells should carry more weight than those in bacterial cells, because mammalian cells are more relevant for understanding any potential effects in humans. Himmelstein *et al*. (2001a) tested the primary metabolite of chloroprene, (1-chloroethenyl)oxirane, and found it to be mutagenic in the absence of S9, suggesting that this metabolite may be the reactive agent in the Ames test; however, this epoxide metabolite was not genotoxic in mammalian cells *in vitro* (Chinese hamster V79 cells) (Himmelstein *et al*. 2001a). Therefore, the results from the Ames test may not be an accurate predictor of carcinogenicity of chloroprene, because glutathione and other detoxification pathways that would mitigate or eliminate the production of potentially active metabolites are not present in S9 microsome preparations at levels present in intact cells. Westphal *et al.* (1994) also found that addition of glutathione to the chloroprene/metabolite Ames tests significantly diminished the reported mutagenic activity. The absence of genotoxicity in intact mammalian cells systems and *in vivo* studies suggests that the bacterial mutagenicity data have limited relevance to the genotoxicity of chloroprene in humans. Critically, and as discussed below, *in vitro* systems do not have the normal levels of detoxifying

pathways found in intact mammalian cells to further metabolize/detoxify this primary metabolite.

4.2.4 Evidence does not support mutagenicity of chloroprene in vivo

The 2010 Review assumed that chloroprene is a point mutagen *in vivo* (in carcinogenicity bioassays with mutations identified in proto-oncogenes). Investigators study mutations in tumors at target sites to identify "mutagen fingerprints" for specific chemicals. As such, Sills *et al.* (1999, 2001) produced a proto-oncogene mutation profile for some target tumors in the mouse. A comparison of chloroprene and 1,3-butadiene indicated that the profile for chloroprene differed from that of 1,3-butadiene. In fact, the mutation rates in chloroprene-exposed animals were similar to mutation rates in control animals. Specific mutations were associated with chloroprene exposures across several different tumor types, but showed no dose-dependency. In contrast, the incidence of lung tumors increased with dose. This indicates that the lung tumors likely are independent of and unrelated to the mutations. These findings suggest that the underlying MOA is not the suspected K-*ras* mutation,[4] but rather a secondary MOA at target sites; for example, an MOA that follows a dose-dependent tumor response that is not associated with a corresponding dose-dependent increase in mutations, such as cytotoxicity-induced bronchiolar hyperplasia. If mutagenicity is the MOA, then mutation rates also should be dose-dependent. This is not the case for chloroprene, where mutations are not shown to be dose-dependent. Therefore, a different MOA is likely.

4.3 Evidence supports an alternative MOA for chloroprene based on cytotoxicity

Despite the inconsistencies in and questionable nature of the evidence for a mutagenic MOA, the 2010 Review never considered alternative MOAs for chloroprene. Considering alternative MOAs is recommended in US EPA's (2005) "Guidelines for Carcinogen Risk Assessment" and is consistent with recommendations by NRC (2011, 2014) for evidence integration and WOE analyses as specified in the Human Relevance Framework (Cohen *et al.* 2003, Meek *et al.* 2003, Cohen 2004, IPCS 2005, Boobis *et al.* 2006). US EPA (2005) guidelines noted that "where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches."

The likely alternative MOA for chloroprene is cytotoxicity, for which there are supportive experimental findings. At very high concentrations, chloroprene is toxic to animals, but does not demonstrate any genotoxicity (Shelby 1990), supporting an MOA based on target-site cytotoxicity. In mice, histopathology evaluations of chloroprene in target tissues are consistent with a non-genotoxic MOA. For example, the incidence of chloroprene-induced bronchiolar hyperplasia in the respiratory system follows the increased incidence of lung tumors, whereas the incidence of lung K-*ras* mutations (a precursor of many cancers) does not. Also, Melnick *et al.* (1996) reported that the toxicity and histopathology observed in

[4] Mutations of the k-*ras* gene are considered an essential step in the development of many cancers (*e.g.*, Jančík *et al.*, 2010).

chloroprene-treated F344 rats and B6C3F1 mice were substantially different from those seen in 1,3-butadiene exposed animals, suggesting an alternative MOA. In this case, a cytotoxicity-driven hyperplasia could be the cause, which can result from cell injury or death and subsequent tissue regeneration. Buzard *et al.* (1996) hypothesized that hyperplastic processes lead to selection of pre-existing oncogene and tumor suppressor gene mutations. Extrapolation from a target-site cytotoxic MOA involving cell proliferation and tumor promotion to other tumor sites is consistent with the attributes of chloroprene. It is important to note that the toxicity of chloroprene is observed at very high concentrations in mice and to a lesser extent in rats; however, it has been confirmed using a validated PBPK model that both species would be expected to be more sensitive to chloroprene exposure than humans. The differences in pharmacokinetics between mice, rats and humans helps to explain the lack of clear evidence of carcinogenicity in humans from epidemiology studies.

4.4 Conclusions

A critical evaluation of the cytotoxic and genotoxic profiles indicated that chloroprene acts through a MOA different from that of 1,3-butadiene, a known human carcinogen. Importantly, chloroprene's genotoxicity profile lacks several attributes necessary to conclude a mutagenic MOA:

- **Standard *in vivo* tests for genotoxicity are negative and unlike known carcinogens such as 1,3-butadiene**: Chloroprene, unlike 1,3-butadiene, is not genotoxic to somatic cells *in vivo.* The study results indicate that the epoxide metabolite of chloroprene is effectively detoxified under *in vivo* exposure conditions.
- **Consistent data are lacking for point mutation induction *in vitro* and *in vivo***: The evidence that chloroprene is able to produce point mutations *in vitro* (specifically in bacteria) is equivocal, and chloroprene did not induce mutations in cultured mammalian cells. There is a clear discordance between findings of *in vitro* point mutation, DNA adduct induction, and *in vivo ras* mutations in target site tumors, which indicate that the observation of these point mutations may not be relevant to the MOA for chloroprene-induced tumors.

Overall, unlike known carcinogens such as 1,3-butadiene, the evidence does not support a mutagenic MOA for chloroprene. Instead, the WOE supports an alternative MOA attributed to site-specific cytotoxicity. Thus, it is neither necessary nor appropriate to adjust the cancer unit risk based on a hypothesized mutagenic MOA, and deriving a new IUR based on an alternative MOA that can be scientifically substantiated is warranted.

5 EPIDEMIOLOGICAL EVIDENCE: OCCUPATIONAL STUDIES

5.1 Evaluation of the epidemiological studies

The 2010 Report classified chloroprene as "likely to be carcinogenic to humans" in part based on US EPA's interpretation of "an association between liver cancer risk and occupational exposure to chloroprene" and "suggestive evidence of an association between lung cancer risk and occupational exposure." As with the evaluation of the toxicological data, US EPA set forth criteria in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) for the evaluation of epidemiological evidence, largely consistent with NRC recommendations (NRC 2014). While US EPA applied some of these criteria in the 2010 Review, US EPA did not present quality assessment and weighting of epidemiological evidence. Our application of these criteria led to largely opposite conclusions: appropriate weighing and synthesis of the epidemiological evidence demonstrated that chloroprene exposure is unlikely to cause lung or liver cancer at the occupational exposure levels encountered in the underlying studies. Furthermore, in contrast with US EPA's interpretation, the lack of any clear cancer risk is consistent with the results from the animal studies demonstrating significant differences across species in the carcinogenic potential of chloroprene, and the mechanistic evidence that humans are far less sensitive to chloroprene.

Using an approach consistent with US EPA (2005) and NRC (2014), Bukowski (2009) evaluated the quality of eight mortality studies of seven chloroprene-exposed cohorts from six countries (Table 5.1). Studies were assigned to categories of high, medium or low quality for each of ten quality criteria and a WOE assessment was performed. The four-cohort Marsh *et al*. (2007a, b) pooled study is the most methodologically rigorous epidemiology study conducted to date. This study has the largest overall cohort size and the most rigorous follow-up. Based on the large cohort size, the Marsh study has the highest statistical power (see Table 5.2). Finally, the Marsh study has the most comprehensive exposure assessment, including assessment of exposure to potentially confounding agents such as vinyl chloride.

Table 5.1. Quality Rankings for Cohort Studies of Cancer Risks from Occupational Chloroprene Exposure

US EPA Criteria	Marsh et al. (2007 a,b) Study				Other Studies			
	Kentucky [1]	North Ireland [1]	Louisiana [1]	France - Mort* [1]	Armenia [2]	France - Incid** [3]	Russia [4]	China [5]
Clear objectives	H‡	H	H	H	H	H-M	H	M
Comparison groups	H	H-M	H-M	M	M	M	M-L	L
Exposure	H	H	H	H	M	M	L	L
Follow-up	H	H-M	H	H-M	M-L	M-L	M-L	M-L
Case ascertainment	H	H-M	H-M	H-M	M	M	M	H-M
Control of bias	H-M	H-M	H-M	M	M-L	M	M	M-L
Sample size	H	H	M	L	M-L	L	H-M	M-L
Data collection and evaluation	H	H	H	H	M	M	M-L	M-L
Adequate response	H	H	H	H	M	M	M	H-M
Documentation of results	H	H	H	H	M-L	M	M	L
Overall rank (1=best)	**1**	**2**	**3**	**4**	**5**	**5**	**5**	**6**

Source: Bukowski 2009 * Mort=Mortality ** Incid=Incidence ‡ Subjective estimate of study quality for each specific criterion H=high, M=medium, L=low; 1 – Marsh *et al*. 2007; 2 – Bulbulyan *et al.* 1999; 3 – Colonna and Laydevant 2001; 4 – Bulbulyan *et al*. 1998; 5 – Li *et al*. 1989

Table 5.2. Relative Size of Marsh *et al*. (2007a, b) Study Compared with Other Available Studies

Study	Subjects (Person-years)	Lung Cancer Deaths	Liver Cancer Deaths
Bulbulyan et al. 1998	5185 (70,328)	31	10
Bulbulyan et al. 1999	2314 (21,107)	3	3
Colonna and Laydevant 2001	717 (17,057)	9	1
Lee and Selevan 1982	Should not be included in the 2010 Review		
Li et al. 1989	1258 (20,105)[a]	2	6
Total Other Studies	**9474 (128,597)**	**45**	**20**
Marsh et al. 2007a (L)	5507 (197,010)	266	17
Marsh et al. 2007a (M)	4849 (127,036)	48	1
Marsh et al. 2007a (P)	1357 (30,660)	12	0
Marsh et al. 2007a (G)	717 (17,057)	10	1
Total Marsh et al. (2007a, b)	**12,430 (372,672)**	**336**	**19**
Combined Studies	**21,904 (501,269)**	**381**	**39**
Marsh et al. (2007a,b) / Combined Studies	**57% (74%)**	**88%**	**49%**

Previously, Rice and Boffetta (2001) reviewed the published epidemiological studies of chloroprene exposed cohorts. Their review included cohorts in the US (Pell 1978), China (Li *et al*. 1989), Russia (Bulbulyan *et al*. 1998), and Armenia

(Bulbulyan *et al*. 1999) and noted significant methodological limitations in these studies, including unclear documentation for cohort enumeration, inadequate reference rates for standardized ratios, a lack of detailed histopathology of liver cancer cases, and limited or no information on potential co-exposures. They also remarked that the occupational chloroprene exposure assessment was poor for all published studies, and the statistical power of the available studies was low due to the small number of observed cancers of interest. Notably, one of the co-authors of the critical review (Boffetta) was also a contributing author of the cohort studies in Russia and Armenia (Bulbulyan *et al*. 1998 and Bulbulyan *et al.* 1999, respectively).

To date, the identified limitations of the studies of Chinese, Russian, and Armenian cohorts remain unaddressed, and most have not been updated. Only the original studies of the US cohort from Louisville, Kentucky (Pell 1978, Leet and Selevan 1982) have been updated and improved. Substantial improvements included detailed descriptions of the cohorts, appropriate comparisons to local cancer rates, an improved exposure assessment both for chloroprene and associated co-exposures (such as vinyl chloride), appropriate follow-up times to capture all potential cancers, appropriate and valid determination of cancer cases, and well-documented methods and results (Marsh *et al.* 2007a, b). A comparison of the study limitations for key quality criteria across the different cohorts is summarized in Table 5.3, and discussed in detail in the next section.

Table 5.3. Comparison of Key Study Criteria across Epidemiological Studies

Key Criteria	US and Europe (Marsh et al. 2007a,b)	Armenia (Bulbulyan et al. 1999)	Russia (Bulbulyan et al. 1998)	China (Li et al. 1989)
Sample Size	French, Irish and US 12,430 (Kentucky ~200,000 person-years)	2,314	5,185	1,258
Follow-up	1949–2000	1979–1993	1979–1993	1969–1983
Exposure Assessment	Exposure modeling – 7 categories	Index (none, low, high)- before/after 1980	Index (none, med, high)- IH (inadequate) + job	High vs. low based on recall
Baseline rates	National, local plant area counties	Armenian rates	Moscow rates	From "local area" 1973–1975
	1960–1994	1980-1989	1979–1993 or	expected lung cancers: 0.4
			1992–1993 (liver)	
Confounding	Used local rate comparisons;	Alcohol use (high cirrhosis rates) and smoking prevalent	Alcohol use (high cirrhosis rates) and smoking;	Hepatitis B and aflatoxin;
	Low prevalence of other liver cancer risk factors		Co-exposure to VCM	Co-exposures to VCM

IH: Industrial hygiene
VCM: vinyl chloride monomer

5.2 Important limitations of the epidemiology literature

The 2010 Review considered lung and liver cancer mortality reported in studies of occupational cohorts from several countries published over 30 years: Pell (1978), Leet and Selevan (1982), Li *et al*. (1989), Bulbulyan *et al*. (1998, 1999), Colonna and Laydevant (2001), and Marsh *et al*. (2007a,b).

Cohort studies comprise a set of data distributed over time to address a hypothesized exposure-disease association (Checkoway *et al*. 2004). In synthesizing results of several cohort studies – or when conducting meta-analyses of such results – it is important to verify that each study cohort is an independent sample and that analytic results are independent, *i.e*., there should be no overlap (e.g., Greenland and O'Rourke 2008). Especially for outcomes with long latency periods and high case-fatality, such as lung and liver cancers, only the most recent and most complete (and non-overlapping) results from cohorts with multiple follow-up periods should be used. Updated results always have more observed person-years at risk and almost always include larger numbers of the health outcome of interest, increasing statistical stability and reducing the probability of chance findings.

The epidemiological literature on chloroprene consists of seven published reports based on nine distinct cohorts. In the 2010 Review, however, *each published epidemiological study* was included as if it were independent, including early results from overlapping or updated cohorts. Specifically, the early results from the Pell (1978) and Leet and Selevan (1982) were included in the most recent update (Marsh *et al*. 2007a, b). Therefore, the Pell (1978) and Leet and Selevan (1982) studies should not have been considered as independent evidence, since all of their cancer deaths were included in the Marsh (2007 a, b) update.

Additionally, the Chinese, Russian, and Armenian studies have serious limitations, as documented by several authors including Rice and Boffetta (2001), Acquavella and Leonard (2001), and Bukowski (2009). As noted above, these studies have not been updated and the noted limitations remain unaddressed. These studies therefore should be given less weight in the synthesis of evidence.

The study of Chinese workers (Li *et al*. 1989) suffered from small numbers of workers, inadequate reference population mortality rates for statistical comparisons, and a lack of adjustment for known causes of lung and liver cancers. The researchers ascertained mortality among 1,213 workers for a 14-year period from 1969 through 1983 and reported 6 deaths due to liver cancer and 2 deaths due to lung cancer. However, they used local mortality rates for only a three-year period (1973 to 1975) to estimate expected numbers of specific cancers. For rare events such as any specific cancer, estimates based on small numbers will be inherently imprecise. Li *et al*. (1989) reported 2.5 and 0.4 expected liver and lung cancer deaths, respectively, among all cohort members followed between 1969 and 1983. The limited number of observed liver and lung cancer deaths divided by the very small expected numbers produced highly imprecise standardized mortality ratios (SMRs) with very large confidence limits. Furthermore, estimates for liver and lung cancer incidence are higher among Chinese men (in 2002, liver cancer mortality was 38 per 100,000 persons per year, and lung cancer mortality was 42 per 100,000 persons per year) and women (liver cancer, 14 per 100,000 persons

per year, and lung cancer, 19 per 100,000 persons per year) (Parkin *et al*. 2005) compared to the rest of the world. In the most high-risk areas of China, 1 in 10 people died of liver cancer (Hsing *et al*. 1991). The major causes of liver cancer in China are chronic infection with hepatitis B virus and aflatoxin B1, in addition to the rising prevalence of alcohol consumption and tobacco smoking (Chen *et al*. 2003, Stuver and Trichopoulos 2008, Lee *et al*. 2009). In contrast, in the US in the years 2009–2013, there were an estimated 9 liver cancer deaths per 100,000 men and 4 liver cancer deaths per 100,000 women per year (SEER 2017). Therefore, observational studies of liver cancer mortality within this Chinese population should control for known causes of these cancers as potential confounding factors. However, the authors of the Chinese study did not control for these confounding factors, and US EPA did not consider the lack of control for confounders when evaluating the quality and weight of the evidence from this study.

Similar to the Li *et al*. (1989) study, Bulbulyan and colleagues (1998) calculated expected numbers of liver cancers using mortality and incidence rates for Moscow for only two years (1992 to 1993), resulting in imprecise reference rates and unstable results. Cancer mortality data from 36 European countries, including the Russian Federation, showed that liver cancer mortality rates among women increased from 1960, peaked during the late 1970s, and declined to their lowest levels during the early 1990s, the period chosen for the study's reference mortality rates (Levi *et al*. 2004). In addition, the Armenian cancer registry is incomplete and may have misclassified the histopathology of reported liver cancers for the general population. Using a reference population with incomplete numbers and mortality rates representative of only a small time period would underestimate the expected incidence and mortality of liver cancer, resulting in over-estimates of the risk estimates. In light of the small numbers and the likelihood that chance may be an explanation for these estimates, the imprecise numbers reported in Bulbulyan *et al*. (1999) and repeated in Zaridze *et al*. (2001) should be viewed skeptically and given little, if any, weight.

The Russian and Armenian cohorts also suffered from inadequate consideration of other major causes of liver cancer. In the populations represented in these cohorts, there is a high incidence of alcoholic cirrhosis, a well-known precursor for liver cancer (London and McGlynn 2006). There were 11 deaths from cirrhosis of the liver (3 in males and 8 in females) recorded for the Russian cohort. In the Armenian cohort, 32 cases of cirrhosis of the liver were reported (27 in males and 5 in females). Alcohol consumption and smoking are well known risks factors for liver cancer, and these factors were not adjusted for in the eastern European cohort studies (Keller 1977, Makimoto and Higuchi 1999, Lee *et al*. 2009). A report by the World Health Organization (WHO 2009) reported a prevalence of 70% and 27% for current tobacco use among Russian men and women, respectively, and noted high levels of alcohol consumption for the general population. The prevalence of current tobacco use among Armenian men is also very high at 55% (WHO 2009). Proper control for these causes was not possible, increasing the likelihood of confounding and thus rendering the results unreliable.

Previous reviews have critiqued the Chinese, Russian, and Armenian studies for inadequate descriptions of the source population rates used to calculate SMRs and standardized incidence ratios (SIRs) (Rice and Boffetta 2001). Another important

methodological concern for the interpretation of SMR and SIR estimates is that when they are based on very small expected values (*i.e.*, less than two), they indicate small population size and/or short follow-up, contributing to unstable estimates (Checkoway, 2004). As such, findings from these studies are not reliable and should carry little if any weight in evaluating cancer causation.

Taken together, the epidemiological studies evaluated in the 2010 Review do not establish a clear causal connection between occupational chloroprene exposure and liver and lung cancers. Consequently, the US EPA's interpretation of the epidemiological evidence as justifying a classification of chloroprene as "likely to be carcinogenic to humans" is questionable. In particular, US EPA's giving the same weight to the large and more robust Marsh *et al*. (2007a, b) epidemiological studies as it gave to the lower quality, lower power studies is inappropriate. Although the Marsh *et al*. (2007a, b) studies have limitations typical of all historical cohort studies, they are the largest studies of potential cancer outcomes with the most complete documentation of exposure. These studies also were designed and conducted specifically to address the limitations previously noted, making the evidence from the Marsh *et al*. (2007a, b) studies far more valid and informative than that from the other studies evaluated by US EPA. The review by Bukowski (2009) (represented in Table 5.1) ranked the study by Marsh *et al.* (2007a, b) as having the highest relative strength based on the same criteria for evaluation listed in the US EPA's "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) and consistent with NRC recommendations (NRC 2011, 2014), and it therefore should be given the greatest weight.

5.3 The Marsh *et al*. (2007a, b) studies do not show a causal link between occupational exposure to chloroprene and increased cancer risks

The Marsh *et al*. (2007 a, b) studies, the most robust epidemiological studies of occupational chloroprene exposure, found no excess of lung or liver cancers (Marsh *et al*. 2007a, b). The 2010 Review, however, stated, "The study involving four plants (including the Louisville Works plant included in the Leet and Selevan (1982) study by Marsh *et al*. (2007a, 2007b), which had the largest sample size and most extensive exposure assessment, also observed increased relative risk estimates for liver cancer in relation to cumulative exposure in the plant with the highest exposure levels (trend p value = 0.09, relative risks [RRs] 1.0, 1.90, 5.10, and 3.33 across quartiles of exposure)." However, the interpretation of these relative risks is more complex than US EPA stated, as the rate of liver cancer deaths among workers was not different from that in the general population.

As shown in Table 5.4, Marsh *et al*. (2007a) computed standardized mortality ratios (SMRs) using national and regional standard populations for the overall cohorts, for selected demographics (males, females, blue-collar workers), and for work histories and exposure factors. The authors concluded that occupational exposures to chloroprene at the levels encountered by each of the cohorts did not show evidence of elevated risk of cancer, including liver cancer.

In a separate publication, Marsh *et al.* (2007b) reported exposure-response data for chloroprene exposure and cancer. In Table 5.5 and Figure 5.1, results for the Louisville plant are shown, including both the internal analyses (relative risks or RRs) and external analyses (SMRs) which are based on comparisons with county

populations. The RRs are the values that US EPA focuses on in their assessment of potential liver cancer risks. However, as noted by Marsh *et al.*, "The elevated RRs result mainly from the exceedingly low death rates associated with the baseline categories of each measure, as reflected by the correspondingly low SMRs (*i.e.*, the RR for a given non-baseline category is roughly related to the ratio of the corresponding SMR for that category to the SMR for the baseline category)."

Table 5.4. Reported Observed Liver Cancer Cases, Expected Counts, and Standardized Mortality Estimates for the Marsh *et al.* 2007a Study

Study Cohort	Observed	Expected*	SMR or SIR	95% Confidence Limits		p-value
				Lower	Upper	
Louisville	17	16.35	1.04	0.61		
Maydown	1	4.17	0.24	0.01		
Pontchartrain	0	--	--	--	--	--
Grenoble	1	1.79	0.56	0.01		
Louisville Subcohorts (local reference)						
Full Cohort	17	18.89	0.9	0.53	1.44	0.78
White race	16	15.69	1.02	0.58	1.65	0.99
Non-White race	1	3.13	0.32	0.01	1.77	0.36
Males	16	17.98	0.89	0.51	1.45	0.75
Females	1	0.94	1.06	0.03	5.93	0.99
Blue collar	17	18.28	0.93	0.54	1.49	0.89
Short-term worker	4	8.16	0.49	0.13	1.26	0.18
Long-term worker	13	10.74	1.21	0.64	2.07	0.57
Duration of employment						
< 5years	4	8.16	0.49	0.13	1.25	0.18
5-19 years	6	3.57	1.68	0.62	3.66	0.30
20+ years	7	7.14	0.98	0.4	2.03	0.99
Time since 1st employment						
< 20 years	1	1.79	0.56	0.01	3.11	0.93
20-29 years	3	3.3	0.91	0.19	2.66	0.99
30 + years	13	13.68	0.95	0.5	1.62	0.99
CD exposure status						
Exposed	17	18.89	0.9	0.53	1.44	0.78

From Marsh *et al.* 2007a

Table 5.5. Exposure-Response Analysis for Chloroprene and Liver Cancers, Based on Internal (Relative Risks) and External (Standardized Mortality Ratio) Estimates, Louisville Plant

Liver cancer	Deaths	Internal Analysis			External Analysis	
		# cases	RR (95% CI)	p-value	Person-years	SMR (95% CI)
Exposure Duration (years)						
<10	6	1500	1.00	Global=0.24	131276	0.61 (0.22-1.32)
10-19	4	216	3.85 (0.75-17.09)	Trend=0.36	30404	2.08 (0.57-5.33)
20+	7	965	1.75 (0.49-6.44)		36239	0.99 (0.40-2.04)
Average Intensity of Exposure (ppm)						
<3.62	3	714	1.00	Global=0.22	69274	0.62 (0.13-1.80)
3.62 - 8.12	7	568	3.81 (0.77-25.76)	Trend=0.84	27933	1.73 (0.70-3.56)
8.12-15.99	3	388	1.84 (0.22-15.74)		28689	0.94 (0.19-2.74)
16.0+	4	1011	1.31 (0.20-10.07)		72023	0.59 (0.16-1.52)
Cumulative exposure (ppm -years)						
<4.75	2	744	1.00	Global=0.17	68918	0.43 (0.05-1.55)
4.75-55.19	3	725	1.9 (0.21-23.81)	Trend=0.09	56737	0.59 (0.12-1.74)
55.91-164.0	7	653	5.1 (0.88-54.64)		39840	1.62 (0.65-3.33)
164.0+	5	559	3.33 (0.48-39.26)		32424	1.00 (0.33-2.34)

From Marsh et al. 2007b; Table 4
CI: confidence interval
ppm: parts per million

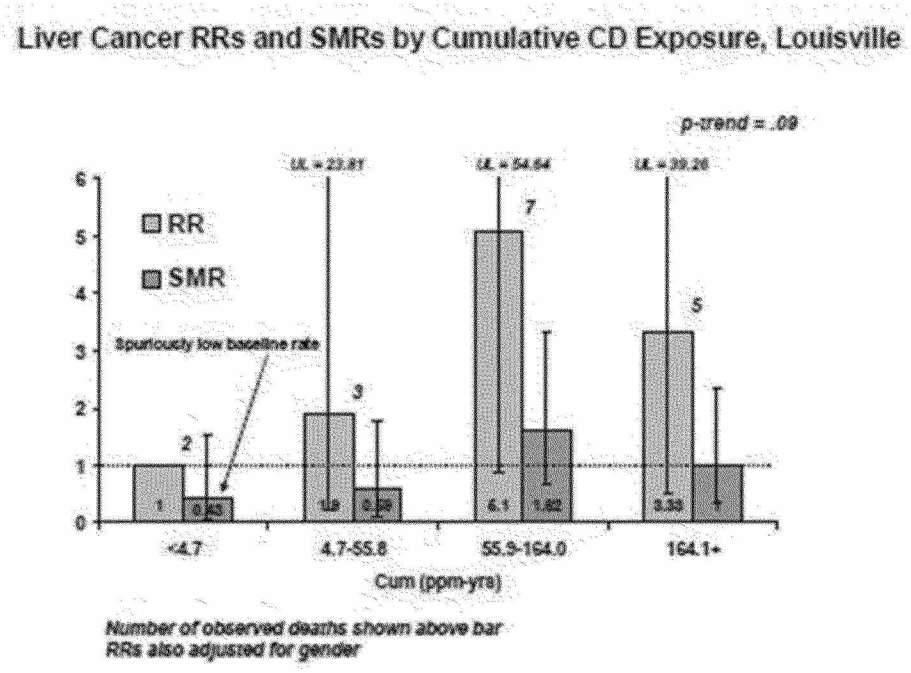

Figure 5.1 Liver Cancer RRs and SMRs by Cumulative Chloroprene Exposure, Louisville

US EPA noted that 3 of the 15 subgroups in Table 5.5 had SMRs greater than 1.00, and inferred from these a likely causal relationship between chloroprene exposure and cancer. However, none of these three SMRs reached statistical significance *(i.e.*, the findings may have been due to chance). In fact, the 95% confidence intervals in Table 5.5 show up to a 10-fold margin of error around the estimated SMRs, underscoring the statistical instability and uncertainty of the risk estimates for these subgroups. In addition, as noted by Marsh *et al*. (2007b), the risk estimates were derived comparing risk from higher exposure groups to risk in the group with the lowest exposure, which had only two liver cancer deaths. The occurrence of only two liver cancer deaths in the lowest exposure group represented a clear deficit in the expected rate of liver cancer, as demonstrated by the SMR (Table 5.5). Comparison to a group with a deficit (most likely due to chance given the small numbers) led to the spurious appearance of an increased risk among the more highly exposed groups. Overall, the chloroprene exposed workers had only about 90% of the expected mortality rate (17 observed with about 19 expected), based on a non-exposed population reference rate (Table 5.4).

Taken as a whole, the epidemiological evidence on chloroprene and cancer is insufficient to conclude that chloroprene is a human carcinogen. The study by Marsh *et al*. (2007a, b) is the largest and methodologically the strongest and, therefore, should carry the greatest weight in integrating the epidemiological evidence for chloroprene. This epidemiological evidence is consistent with the toxicological hypothesis that humans are less sensitive than animals to the possible carcinogenic effects of chloroprene, and also supports the conclusion by Allen *et al*. (2014) that a modified cancer unit risk that accounts for animal-to-human extrapolations is needed.

6 CANCER CLASSIFICATION FOR CHLOROPRENE

The 2010 Review determined that chloroprene was "likely to be carcinogenic to humans" based on EPA's conclusions of (1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) a proposed mutagenic mode of action (MOA); and (5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride. As has been demonstrated in this report, three of the five EPA conclusions are not supported by the weight of evidence, and the fourth—structural similarities —has been shown not to be informative, as the chemicals demonstrate different modes of action. Based on the limited evidence remaining to support the potential carcinogenicity of chloroprene, we conclude that a more appropriate classification of chloroprene is "suggestive evidence of carcinogenic potential."

To classify a chemical as "likely to be carcinogenic to humans," US EPA notes that "this descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "carcinogenic to humans (US EPA, 2005)." Adequate evidence consistent with this descriptor covers a broad spectrum and as noted by US EPA (2005), "choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence." Strong evidence for carcinogenicity in humans is not needed; however, the weight of evidence is still required to support the classification descriptor.

In the 2010 Review, the weight of evidence narrative provided for chloroprene to support the descriptor of "likely to be carcinogenic to humans" was limited to a check-list provided above (US EPA, 2010a, pg. 96 and Table 4-39). However, in reviewing the underlying data for the evidence presented in this checklist, we note that only two of the five can be substantiated: (1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data, and (5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride.

We have demonstrated considerable misinterpretation in the 2010 Review of the available science to support other items on the checklist. For example, the epidemiological evidence, based on an appropriate weight of evidence approach, fails to demonstrate clearly increased risks among exposed occupational groups and the general population, and a weak difference between exposed and unexposed workers reflecting a deficit among the least exposed (see Section 5). The claim that chloroprene is mutagenic is not supported by the overall evidence from the available data, as discussed in Section 4. Although there are structural similarities of chloroprene and 1,3-butadiene and vinyl chloride, the toxicological evidence including possible modes of action (MOAs) demonstrate substantial differences between chloroprene, vinyl chloride, and 1,3-butadiene.